

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

REC'D 08 APR 2005



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| Applicant's or agent's file reference X-15985 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US 03/1513 | International filing date (day/month/year) 24.10.2003 | Priority date (day/month/year) 05.11.2002 |
| International Patent Classification (IPC) or both national classification and IPC C07C217/62 | | |
| Applicant ELI LILLY AND COMPANY et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

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|---|---|
| Date of submission of the demand 28.04.2004 | Date of completion of this report 07.04.2005 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Österle, C Telephone No. +49 89 2399-8120  |

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 03/1513

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, Pages

1-147 as originally filed

Claims, Numbers

1-44 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Indicate whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious) or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☐ the claims Nos. 1-16 and 19-44 in part

because:

☐ the said international application, or the said claims Nos. 40-44 (for industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-16 and 19-44 in part

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

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- ☒ all parts.
☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

| | | |
|-------------------------------|-------------|--------|
| Novelty (N) | Yes: Claims | 1-44 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 2 |
| | No: Claims | 1,3-44 |
| Industrial applicability (IA) | Yes: Claims | 1-39 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 40-44 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
2. Claims or parts of claims relating to compounds for which X is not unsubstituted or substituted phenyl have not been subject to search. Parts of the claims for which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). No opinion with regard to novelty and inventive step therefore has been established for subject-matter of claims 1-16 (in part) and 19-44 (in part).

Re Item IV

Lack of unity of invention

In order to satisfy the requirement of unity compounds cover by a Markush-formula must have a significant structural element in common. Furthermore, this common part of the structure must distinguish the compounds from any known compounds having the same property/activity.

The structural element common to all compounds of present claim 1 is the skeleton CH-CH-CH₂-NR₁R₂.

This structural element is however known for compounds of the prior art having the same activity (see for example XP 000605241, EP 0373836).

Present claim 1 therefore lacks unity (Rule 13.1 PCT).

The following groups of inventions therefore are not so linked as to form a single general inventive concept:

1. compounds wherein Z=F (claims 1-13 (in part), 14,17-44 (in part))

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2. compounds wherein $Z=OH$ (claims 1-13 (in part), 15, 17-44 (in part))
3. compounds wherein $Z=OAlk$ (claims 1-13 (in part), 16, 17-44 (in part))

Furthermore, since compounds for which $Z=OH$ or $OALK$ are also known from XP000605241, groups 2 and 3 are subdivided into inventions in which each invention is defined by one of the definitions of Y as claimed in claim 1.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1: MELLONI P ET AL: "POTENTIAL ANTIDEPRESSANT AGENTS-ALPHA-ARYLOXY-BENZYL DERIVATIVES OF ETHANOLAMINE AND MORPHOLINE" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 19, no. 3, 1984, pages 235-242, XP000605241 ISSN: 0223-5234
- D2: EP-A-0 373 836 (LILLY CO ELI) 20 June 1990 (1990-06-20)

1. Novelty (Article 33(2) PCT):

- 1.1 D1 discloses norepinephrine uptake inhibitors of formula (I). The compounds of D1 differ from the compounds of present claim 1 in that $A=O$.
- 1.2 D2 (EP 0 373 836) discloses serotonin and norepinephrine uptake inhibitors of formula (I). The compounds of D2 differ from the compounds of present claim 1 in that $Z=H$ in D2.
- 1.3 The subject-matter of claims 1-44 then can be considered novel.

2. Inventive Activity (Article 33(3) PCT):

- 2.1 Starting from D1 as the closest prior art, the technical problem can be seen in providing improved compounds which are serotonin and norepinephrine uptake inhibitors.

The solution suggested by the applicant then would be the replacement of an oxygen atom with a sulfur atom. This substitution is, in absence of a technical effect linked to this exchange considered obvious to the person skilled in the art, since ethers and thioethers can be expected to have the same or similar properties.

Even if one would considered this exchange non-obvious, the person skilled in the art would derive from D2 that exchanging O for S results in compound which have the same activity.

The subject-matter of claims 1, 3-44 therefore cannot be considered inventive.

- 2.2 Regarding the subject-matter of claim 2, when A=O Y cannot be optionally substituted phenyl or optionally substituted 1,3-benzodioxolyl when Z is OR₃ (proviso of claim 1).

The difference between D1 and claim 2 then is for example that Y is a different aromatic substituent.

D1 or D2 do not suggest compounds for which Y is an aromatic substituent different from phenyl.

In view of D1 and D2 the subject-matter of claim 2 therefore can be considered inventive.

3. Industrial Applicability (Article 33(4) PCT):

- 3.1 The subject-matter of claims 1-39 is industrially applicable.